

University of Dundee

Trans-ethnic association study of blood pressure determinants in over 750,000 individuals

Understanding Society Scientific Group; Giri, Ayush; Hellwege, Jacklyn N.; Keaton, Jacob M.; Park, Jihwan; Qiu, Chengxiang

Published in:
Nature Genetics

DOI:
[10.1038/s41588-018-0303-9](https://doi.org/10.1038/s41588-018-0303-9)

Publication date:
2019

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Understanding Society Scientific Group, Giri, A., Hellwege, J. N., Keaton, J. M., Park, J., Qiu, C., Warren, H. R., Torstenson, E. S., Kovesdy, C. P., Sun, Y. V., Wilson, O. D., Robinson-Cohen, C., Roumie, C. L., Chung, C. P., Birdwell, K. A., Damrauer, S. M., DuVall, S. L., Klarin, D., Cho, K., ... Edwards, T. L. (2019). Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nature Genetics*, 51(1), 51-62. <https://doi.org/10.1038/s41588-018-0303-9>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Acknowledgements and funding statements

Million Veteran Program (MVP):

MVP Executive Committee

- Co-Chair: J. Michael Gaziano, M.D., M.P.H.
- Co-Chair: Rachel Ramoni, D.M.D., Sc.D.
- Jim Breeling, M.D. (ex-officio)
- Kyong-Mi Chang, M.D.
- Grant Huang, Ph.D.
- Sumitra Muralidhar, Ph.D.
- Christopher J. O'Donnell, M.D., M.P.H.
- Philip S. Tsao, Ph.D.

MVP Program Office

- Sumitra Muralidhar, Ph.D.
- Jennifer Moser, Ph.D.

MVP Recruitment/Enrollment

- Recruitment/Enrollment Director/Deputy Director, Boston – Stacey B. Whitbourne, Ph.D.; Jessica V. Brewer, M.P.H.
- MVP Coordinating Centers
 - o Clinical Epidemiology Research Center (CERC), West Haven – John Concato, M.D., M.P.H.
 - o Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque - Stuart Warren, J.D., Pharm D.; Dean P. Argyles, M.S.
 - o Genomics Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D.
 - o Massachusetts Veterans Epidemiology Research Information Center (MAVERIC), Boston - J. Michael Gaziano, M.D., M.P.H.
 - o MVP Information Center, Canandaigua – Brady Stephens, M.S.
- Core Biorepository, Boston – Mary T. Brophy M.D., M.P.H.; Donald E. Humphries, Ph.D.
- MVP Informatics, Boston – Nhan Do, M.D.; Shahpoor Shayan
- Data Operations/Analytics, Boston – Xuan-Mai T. Nguyen, Ph.D.

MVP Science

- Genomics - Christopher J. O'Donnell, M.D., M.P.H.; Saiju Pyarajan Ph.D.; Philip S. Tsao, Ph.D.
- Phenomics - Kelly Cho, M.P.H, Ph.D.
- Data and Computational Sciences – Saiju Pyarajan, Ph.D.
- Statistical Genetics – Elizabeth Hauser, Ph.D.; Yan Sun, Ph.D.; Hongyu Zhao, Ph.D.

MVP Local Site Investigators

- Atlanta VA Medical Center (Peter Wilson)
- Bay Pines VA Healthcare System (Rachel McArdle)
- Birmingham VA Medical Center (Louis Dellitalia)
- Cincinnati VA Medical Center (John Harley)
- Clement J. Zablocki VA Medical Center (Jeffrey Whittle)
- Durham VA Medical Center (Jean Beckham)
- Edith Nourse Rogers Memorial Veterans Hospital (John Wells)
- Edward Hines, Jr. VA Medical Center (Salvador Gutierrez)
- Fayetteville VA Medical Center (Gretchen Gibson)
- VA Health Care Upstate New York (Laurence Kaminsky)
- New Mexico VA Health Care System (Gerardo Villareal)
- VA Boston Healthcare System (Scott Kinlay)
- VA Western New York Healthcare System (Junzhe Xu)
- Ralph H. Johnson VA Medical Center (Mark Hamner)
- Wm. Jennings Bryan Dorn VA Medical Center (Kathlyn Sue Haddock)
- VA North Texas Health Care System (Sujata Bhushan)
- Hampton VA Medical Center (Pran Iruvanti)
- Hunter Holmes McGuire VA Medical Center (Michael Godschalk)
- Iowa City VA Health Care System (Zuhair Ballas)
- Jack C. Montgomery VA Medical Center (Malcolm Buford)
- James A. Haley Veterans' Hospital (Stephen Mastorides)
- Louisville VA Medical Center (Jon Klein)
- Manchester VA Medical Center (Nora Ratcliffe)
- Miami VA Health Care System (Hermes Florez)
- Michael E. DeBakey VA Medical Center (Alan Swann)
- Minneapolis VA Health Care System (Maureen Murdoch)
- N. FL/S. GA Veterans Health System (Peruvemba Sriram)
- Northport VA Medical Center (Shing Shing Yeh)
- Overton Brooks VA Medical Center (Ronald Washburn)
- Philadelphia VA Medical Center (Darshana Jhala)
- Phoenix VA Health Care System (Samuel Aguayo)
- Portland VA Medical Center (David Cohen)
- Providence VA Medical Center (Satish Sharma)
- Richard Roudebush VA Medical Center (John Callaghan)
- Salem VA Medical Center (Kris Ann Oursler)
- San Francisco VA Health Care System (Mary Whooley)
- South Texas Veterans Health Care System (Sunil Ahuja)
- Southeast Louisiana Veterans Health Care System (Amparo Gutierrez)

- Southern Arizona VA Health Care System (Ronald Schiffman)
- Sioux Falls VA Health Care System (Jennifer Greco)
- St. Louis VA Health Care System (Michael Rauchman)
- Syracuse VA Medical Center (Richard Servatius)
- VA Eastern Kansas Health Care System (Mary Oehlert)
- VA Greater Los Angeles Health Care System (Agnes Wallbom)
- VA Loma Linda Healthcare System (Ronald Fernando)
- VA Long Beach Healthcare System (Timothy Morgan)
- VA Maine Healthcare System (Todd Stapley)
- VA New York Harbor Healthcare System (Scott Sherman)
- VA Pacific Islands Health Care System (Gwenevere Anderson)
- VA Palo Alto Health Care System (Philip Tsao)
- VA Pittsburgh Health Care System (Elif Sonel)
- VA Puget Sound Health Care System (Edward Boyko)
- VA Salt Lake City Health Care System (Laurence Meyer)
- VA San Diego Healthcare System (Samir Gupta)
- VA Southern Nevada Healthcare System (Joseph Fayad)
- VA Tennessee Valley Healthcare System (Adriana Hung)
- Washington DC VA Medical Center (Jack Lichy)
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley)
- White River Junction VA Medical Center (Brooks Robey)
- William S. Middleton Memorial Veterans Hospital (Robert Striker)

GoDARTS

Acknowledgements and Funding

The Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (GoDARTS) was funded by The Wellcome Trust (072960/Z/03/Z, 084726/Z/08/Z, 084727/Z/08/Z, 085475/Z/08/Z, 085475/B/08/Z) and as part of the EU IMI-SUMMIT program.

The Women's Genome Health Study (WGHS)

Acknowledgements and Funding

WGHS is supported by the National Heart, Lung, and Blood Institute (HL043851 and HL080467) and the National Cancer Institute (CA047988 and UM1CA182913) with collaborative scientific support and funding for genotyping provided by Amgen. JUPITER: The JUPITER trial was funded by AstraZeneca, who also provided collaborative support for genotyping.

Malmö Diet and Cancer Study

Acknowledgements and Funding

Malmö Diet and Cancer Study received funding by the Knut and Alice Wallenberg Foundation.

Netherlands Epidemiology in Obesity (NEO)

Acknowledgements and Funding

The authors of the NEO study thank all individuals who participated in the Netherlands Epidemiology in Obesity study, all participating general practitioners for inviting eligible participants and all research nurses for collection of the data. We thank the NEO study group, Pat van Beelen, Petra Noordijk and Ingeborg de Jonge for the coordination, lab and data management of the NEO study. The genotyping in the NEO study was supported by the Centre National de Génotypage (Paris, France), headed by Jean-Francois Deleuze. The NEO study is supported by the participating Departments, the Division and the Board of Directors of the Leiden University Medical Center, and by the Leiden University, Research Profile Area Vascular and Regenerative Medicine. Dennis Mook-Kanamori is supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023).

CROATIA_Vis ,CROATIA_Korcula and CROATIA_Split

Acknowledgements and Funding

The CROATIA_Vis ,CROATIA_Korcula and CROATIA_Split studies were funded by grants from the Medical Research Council (UK), European Commission Framework 6 project EUROSPAN (Contract No. LSHG-CT-2006-018947) and Republic of Croatia Ministry of Science, Education and Sports research grants. (108-1080315-0302). We would like to acknowledge the staff of several institutions in Croatia that supported the field work, including but not limited to The University of Split and Zagreb Medical Schools, Institute for Anthropological Research in Zagreb and Croatian Institute for Public Health.

Generation Scotland

Acknowledgements and Funding

Generation Scotland received core funding from the Chief Scientist Office of the Scottish Government Health Directorate CZD/16/6 and the Scottish Funding Council HR03006. Genotyping of the GS:SFHS samples was carried out by staff at the Genetics Core Laboratory at the Clinical Research Facility, University of Edinburgh, Scotland and was funded by the Wellcome Trust 104036/Z/14/Z (STRADL, Stratifying Resilience and Depression Longitudinally) and the UK's Medical Research Council. We thank all families and practitioners involved in the recruitment process as well as the entirety of Generation Scotland team; interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants and nurses.

TwinsUKstudy

Acknowledgements and Funding

The TwinsUK study was funded by the Wellcome Trust, Medical Research Council, and European Union. The study also receives support from the National Institute for Health Research (NIHR) BioResource Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. SNP Genotyping was performed by The Wellcome Trust Sanger Institute and National Eye Institute via NIH/CIDR.

KWLPS (Gambia) cohort

Acknowledgements and funding.

The KWLPS (Gambia) cohort is supported through funding was received from the UK Medical Research Council (MRC) and the UK Department for International Development (DFID), under the MRC/DFID Concordat agreement (MC-A760-5QX00, U105960371 and U123261351). We thank all residents of the villages of Kiang West, The Gambia, for their willingness to participate in our studies. Thanks also go to field, laboratory, clinical, data, and administrative staff at MRC Keneba, and in particular Mohammed Ngum as well as past and present members of the Keneba Biobank team, who facilitated the collection and processing of data and samples in The Gamiba that form the basis of these analyses. Thanks are further due to Josyf C Mychaleckyj and Uma Nayak (University of Virginia, USA), Matt Silver and Modou Jobe (MRC Unit The Gambia), Vickie S. Braithwaite (MRC Human Nutrition Research, Cambridge, UK) and Kerra Pearce (UCL Genomics) for their assistance with genotyping and/or data analyses.

Avon Longitudinal Study of Parents and Children Study (ALSPAC)

Acknowledgements and funding

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. NJT is a Wellcome Trust Investigator (202802/Z/16/Z), is a programme lead in the MRC Integrative Epidemiology Unit (MC_UU_12013/3) and works within the University of Bristol NIHR Biomedical Research Centre (BRC). TGR is a UKRI Innovation Research Fellow (MR/S003886/1).

Hellenic Isolated Cohorts - Minoan Isolates Study

Acknowledgements and funding

Hellenic Isolated Cohorts - Minoan Isolates Study was funded by the Wellcome Trust (098051) and the European Research Council (ERC-2011-StG 280559-SEPI). The MANOLIS cohort is named in honour of Manolis Giannakakis, 1978-2010. We thank the residents of the Mylopotamos villages for taking part. The HELIC study has been supported by many individuals who have contributed to sample collection (including A. Athanasiadis, O. Balafouti, C. Batzaki, G. Daskalakis, E. Emmanouil, C. Giannakaki, M. Giannakopoulou, A. Kaparou, V. Kariakli, S. Koinaki, D. Kokori, M. Konidari, H. Koundouraki, D. Koutoukidis, V. Mamakou, E. Mamalaki, E. Mpamiaki, M. Tsoukana, D. Tzakou, K. Vosdogianni, N. Xenaki, E. Zengini), data entry (T. Antonos, D. Papagrigoriou, B. Spiliopoulou), sample logistics (S. Edkins, E. Gray), genotyping (R. Andrews, H. Blackburn, D. Simpkin, S. Whitehead), research administration (A. Kolb-Kokocinski, S. Smee, D. Walker) and informatics (M. Pollard, J. Randall).

Cardiovascular Health Study (CHS)

Acknowledgements and funding

CHS research was supported by NHLBI contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086; and NHLBI grants U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and R01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by CTSI grant UL1TR000124 and DK063491. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Individual Acknowledgements and funding

Jacklyn N. Hellwege, Ayush Giri, Adriana Hung, and Todd L. Edwards were supported by NIH/NHLBI grant HL121429 (to TLE) and VA grant 1I01CX000982 & I01BX003360 (to AH). This research is based on data from the Million Veteran Program, Office of Research and Development, Veterans Health Administration, and was supported by award # [I01BX003360]. This work was supported using resources and facilities of the VA Informatics and Computing Infrastructure (VINCI), VA HSR RES 13-457. This publication does not represent the views of the Department of Veterans Affairs or the United States Government. Philip S. Tsao, and Scott M. Damrauer were funded by the *Genetics of Cardiometabolic Diseases in the VA Population* Veterans Affairs Office of Research and Development (BX-003362-01) grant. Peter Wilson was funded by the Veterans Affairs Merit Award I01-01BX003340 (Wilson)

Digna R. Velez Edwards received support from NIH/NHLBI (HL121429). Jacklyn N. Hellwege and Brian S. Mautz were supported by the Vanderbilt Molecular and Genetic Epidemiology of Cancer (MAGEC) training program, funded by T32CA160056 (PI: X.-O. Shu).

Jacob M Keaton is supported by the Vanderbilt Genomic Medicine Training Program. The Vanderbilt Genomic Medicine Training Program is supported by an institutional training grant (T32HG008341) from the National Human Genome Research Institute of the National Institute of Health.

Yan V. Sun was supported by Veterans Affairs Merit Award I01-BX003340 (to PFWF) and NIH grant NR013520.

Cassianne Robinson-Cohen was supported by NIH/NIDDK K01DK109019.

Cecilia P. Chung was supported by K23AR064768 (NIAMS), and the Rheumatology Research Foundation.

Louise Wain holds a GSK / British Lung Foundation Chair in Respiratory Research. This Article presents independent research funded partially by the UK National Institute for Health Research (NIHR). The views expressed are our own and not necessarily those of the NHS, the NIHR, or the UK Department of Health.

Stéphanie Debette was supported for this work by grants from the European Research Council (ERC), the EU Joint Programme - Neurodegenerative Disease Research (JPND), from the European Union's Horizon 2020 research and innovation programme under grant agreements No 643417 & No 640643, and by the Agence Nationale de la Recherche (ANR).

Eleftheria Zeggini was supported by the Wellcome Trust (WT098051).

Patricia Munroe was supported by the Medical Research Council of Great Britain (grant number G9521010D); and by the British Heart Foundation (grant number PG/02/128). Martin Farrall acknowledges support from the Wellcome Trust core award (090532/Z/09/Z) and the Oxford British Heart foundation Centre for Research Excellence (RE/13/1/30181). A.F.D. was supported by the British Heart Foundation (grant numbers RG/07/005/23633, SP/08/005/25115); and by the European Union Ingenious HyperCare Consortium: Integrated Genomics, Clinical Research, and Care in Hypertension (grant number LSHM-C7-2006-037093). The BRIGHT study is extremely grateful to all the patients who participated in the study and the BRIGHT nursing team. This work forms part of the research portfolio for the National Institute for Health Research Barts Biomedical Research Centre.

Peter Sever is the recipient of NIHR Senior Investigator Award. Peter Sever and Neil R Poulter were supported by Pfizer, New York, NY, USA, for the ASCOT study and the collection of the ASCOT DNA repository; by Servier Research Group, Paris, France; and by Leo Laboratories, Copenhagen, Denmark. We thank all ASCOT trial participants, physicians, nurses, and practices in the participating countries for their important contribution to the study. In particular, we thank Clare Muckian and David Toomey for their help in DNA extraction, storage, and handling. This work forms part of the research programme of the NIHR Cardiovascular Biomedical Research Unit at Barts.

Joanna M.M. Howson, Praveen Surendran, and Savita Karthikeyan was supported by UK Medical Research Council (G0800270), British Heart Foundation (SP/09/002), UK National Institute for Health Research Cambridge Biomedical Research Centre, European Research Council (268834), European Commission Framework Programme 7 (HEALTH-F2-2012-279233). We thank all EPIC participants and staff for their contribution to the study, the laboratory teams at the Medical Research Council Epidemiology Unit for sample management and Cambridge Genomic Services for genotyping, Sarah Spackman for data management, and the team at the EPIC-CVD Coordinating Centre for study coordination and administration.

Nicholas Wareham and Claudia Langenberg were supported by Medical Research Council UK (G1000143; MC_UU_12015/1; MC_PC_13048; MC_U106179471), Cancer Research UK (C864/A14136), EU FP6 programme (LSHM_CT_2006_037197).

Sébastien Thériault was supported by Canadian Institutes of Health Research; Laval University (Quebec City, Canada).

John Attia and Christopher Oldmeadow would like to acknowledge the Vincent Fairfax Family Fund, the University of Newcastle Strategic Initiative Fund and all the participants who volunteered their time.

Pim van der Harst was supported by Marie Skłodowska-Curie GF (call: H2020-MSCA-IF-2014, Project ID: 661395).

Niek Verweij was supported by Marie Skłodowska-Curie GF (call: H2020-MSCA-IF-2014, Project ID: 661395) and NWO VENI (016.186.125).

David Schlessinger was supported by Intramural Research Program of the National Institute on Aging, NIH.

Marjo-Riitta Jarvelin and Karl-Heinz Herzig were supported by NFBC1966 and NFBC1986: NFBC1966 and 1966 received financial support from the Academy of Finland (project grants 104781, 120315, 129269, 1114194, 24300796, Center of Excellence in Complex Disease Genetics and SALVE), University Hospital Oulu, Biocenter, University of Oulu, Finland (75617), NIHM (MH063706, Smalley and Jarvelin), Juselius Foundation, NHLBI grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02), the European Commission (EURO-BLCS, Framework 5 award QLG1-CT-2000-01643), ENGAGE project and grant agreement HEALTH-F4-2007-201413, EU FP7 EurHEALTHAgeing -277849, the Medical Research Council, UK (G0500539, G0600705, G1002319, PrevMetSyn/SALVE) and the MRC, Centenary Early Career Award. The program is currently being funded by the H2020 DynaHEALTH action (grant agreement 633595) and academy of Finland EGEA-project (285547). The DNA extractions, sample quality controls, biobank up-keeping and aliquotting was performed in the National Public Health Institute, Biomedicum Helsinki, Finland and supported financially by the Academy of Finland and Biocentrum Helsinki. We thank the late Professor Paula Rantakallio (launch of NFBCs), and Ms

Outi Tornwall and Ms Minttu Jussila (DNA biobanking). The authors would like to acknowledge the contribution of the late Academician of Science Leena Peltonen.

Paul Elliott acknowledges support from the Medical Research Council (MRC) and Public Health England (PHE) Centre for Environment and Health (MR/L01341X/1), and additional support from the NIHR Biomedical Research Centre at Imperial College Healthcare NHS Trust and Imperial College London, and the NIHR Health Protection Research Unit in Health Impact of Environmental Hazards (HPRU-2012-10141). This work used computing resources of the UK MEDical BIOinformatics partnership- (UK MED-BIO) supported by the Medical Research Council (MR/L01632X/1). P.E. is a UK Dementia Research Institute (DRI) professor, UK DRI at Imperial College London, funded by the MRC, Alzheimer's Society and Alzheimer's Research UK and an Associate Professor of the London Health Data Research UK Centre.

Cecilia Lindgren received funding from Wellcome Trust (086596/Z/08/Z) and is supported by Li Ka Shing Foundation, WT-SSI/John Fell funds, the NIHR Biomedical Research Centre, Oxford, Widenlife and NIH (5P50HD028138-27)

Christopher Newton_chen was Supported by R01HL113933 and R01HL124262.

Daniel Chasman received funding for genotyping of the exome chip and collaborative scientific support from Amgen.

Najim Lahrouchi received support from The Dutch Heart Foundation CVON-PREDICT project (CVON2012-10).

Wei-Qi Wei received funding from NIH R01 (R01 HL133786)

Helen R. Warren was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Unit at Barts and The London School of Medicine and Dentistry.

Claudia P. Cabrera was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Unit at Barts and The London School of Medicine and Dentistry.

Mark J. Caulfield was funded by the National Institute for Health Research (NIHR) as part of the portfolio of translational research of the NIHR Biomedical Research Unit at Barts and The London School of Medicine and Dentistry. M.J.C. is a National Institute for Health Research (NIHR) senior investigator.

Yaomin Xu and Yu Wang were supported by the Biostatistics Development Award of the Department of Biostatistics of Vanderbilt University Medical Center.

Katalin Susztak was funded by R01DK076077, R01DK087635 and DP3DK108220.

Michael Boehnke and Laura J Scott were funded by DK062370.

One of the datasets used for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by institutional funding, the 1S10RR025141-01 instrumentation award, and by the CTSA grant UL1TR000445 from NCATS/NIH. Additional funding provided by the NIH through grants P50GM115305 and U19HL065962. The authors wish to acknowledge the expert technical support of the VANTAGE and VANGARD core facilities, supported in part by the Vanderbilt-Ingram Cancer Center (P30 CA068485) and Vanderbilt Vision Center (P30 EY08126).